UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,451	12/20/2001	Jesper Z. Haeggstrom	PVZ-006USRCE	4167

959 7590 11/25/2008

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,451	HAEGGSTROM ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,61,68,70-72,76,78 and 79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,61,68,70-72,76,78 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 02/22/2008), Applicants filed a response and amendment received on 08/22/2008. Said amendment cancelled Claims 1-59, 62-67, 69, 73-75, 77 and 80-86; amended Claims 60 and 70.

Claims 60-61, 68, 70-72, 76 and 78-79 are pending in the instant office action and will be examined herein.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

2. Claims 60-61, 68, 70-72, 76 and 78-79 are rejected under 35 U.S.C. 112, first paragraph, **new matter**, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 60 (Claims 61, 68 dependent therefrom) and Claim 70 (Claims 71-72, 76 and 78-79 dependent therefrom) recite the limitation of a buffer solution and an enzyme solution having "about 28% PEG8000", "about 0.1 M Na-acetate", "about 0.1 M

imidazole", "pH of about 6.8", "about 5 mM $YbCl_3$", "about 5 mg/ml LTA4 hydrolase", "about 10 mM Tris-HCl", "pH of about 8" and "about 1 mM bestatin". The recited constituents are disclosed in the specification, on page 36. However, the recited limitations for buffer and enzyme solutions with the term "about" are not supported by the original disclosure. The applicant is advised to point out the support in the original disclosure or amend the instant claims.

3. Claims 60-61, 68, 70-72, 76 and 78-79 are rejected under 35 U.S.C. § 112, first paragraph, **written description**, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 60-62, 68, 70-72, 76 and 78-86. In response to this rejection, applicants have cancelled Claims 1-59, 62-67, 69, 73-75, 77 and 80-86; amended Claims 60 and 70; and traverse the rejection as it applies to the newly amended claims.

Applicants submit that in view of their discovery of a method for crystallizing the LTA4 hydrolase, and in view of the teachings of the specification, one skilled in the art would appreciate that Applicants were in possession of the claimed invention at the time of filing of the present application; and argue that instant amendment in accordance with

the Examiner's recommendation, to specifically recite the crystallization conditions set forth in the specification; thereby rendering the foregoing rejection moot.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The examiner notes that instant amendments recite constituents of the buffer solution and the enzyme solution used in a method of crystallizing the protein of SEQ ID NO: 1. Contrary to Applicants' argument, the recited term "about" and/or "comprising" makes the instant method claims much broader than the crystallization conditions disclosed in the specification on page 36. Also, the recitation of the open term "comprising" for a buffer solution and an enzyme solution is so broad as to encompass many additional compounds in the solutions. As previously noted on page 7, lines 3-9, "In general, for a species of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the precipitant solution(s)." The method of crystallization encompassed by the breadth of the claims is not adequately described because a singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege et al. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). The method having crystallization condition to crystallize any

protein comprising SEQ ID NO: 1 in the presence of about 1mM bestatin and any other composition added beside recited constituents in Claims 60 and 70 cannot be sufficiently described by the instant disclosure of specification on page 36. Thus, in view of the teachings of the specification, one skilled in the art would recognize that Applicants were in possession of the full scope of claimed invention at the time of filing of the present application.

4. Claims 60-62, 68, 70-72, 76 and 78-86 are rejected under 35 U.S.C. § 112, first paragraph, **scope of enablement**, because the specification, while being enabling for a method comprising crystallization of SEQ ID NO: 1 in the presence of bestatin by the condition described on page 36, lines 3-19, that results in a crystal having the space group P21212 and the unit cell dimensions a=67.59 Å, b=133.51 Å, c=83.40 Å and $\alpha=\beta=\gamma=90^{o}$; does not reasonably provide enablement for a method comprising crystallization of SEQ ID NO: 1; wherein the crystallization is performed with any buffer solution as long as it contains about 28% PEG8000, about 0.1 M Na-acetate, about 0.1 M imidazole at a pH of about 6.8 and with about 5 mM YbC13 as an additive; and any enzyme solution as long as it contains about 5 mg/ml LTA4 hydrolase comprising the amino acid sequence of SEQ ID NO: 1 (i.e., any protein or fusion protein as long as it contains SEQ ID NO: 1) in about 10 mM Tris-HC1 at a pH of about 8, supplemented with about 1 mM bestatin; wherein the buffer solution and the enzyme solution can have any other additional constituents (e.g., compounds, molecules or proteins).

The rejection was stated in the previous office action as it applied to previous Claims 60-62, 68, 70-72, 76 and 78-86. In response to this rejection, applicants have cancelled Claims 1-59, 62-67, 69, 73-75, 77 and 80-86; amended Claims 60 and 70; and traverse the rejection as it applies to the newly amended claims.

Applicants submit that in view of their discovery of a method for crystallizing the LTA4 hydrolase, and in view of the teachings of the specification, one skilled in the art would be able to make and use the claimed invention using only routine experimentation; and argue that instant amendment in accordance with the Examiner's recommendation, to specifically recite the crystallization condition set forth in the specification; thereby rendering the foregoing rejection moot.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The examiner notes that instant amendments recite constituents of the buffer solution and the enzyme solution used in a method of crystallizing the protein of SEQ ID NO: 1. Contrary to the Applicants' argument, the recited term "about" and/or "comprising" makes the instant method claims much broader than the crystallization condition disclosed in the specification on page 36. Also, the recitation of the open term "comprising" for a buffer solution and an enzyme solution is broad to encompass any other additional compounds in the solutions. As previously noted on page 10, lines 8-12, methods of protein crystallization were well known in the art, but the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth.

Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict a priori those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, Biophys Chem 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle), as noted in the previous office action, page 11. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is very high and a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to crystallization of any protein comprising SEQ ID NO: 1 (e.g., any fusion protein containing the SEQ ID NO: 2) can be crystallized under a different set of crystallization parameters disclosed in Claims 60 and 70 (e.g. any buffer or enzyme solution with any additional constituents as long as it contains the chemicals recites in Claims 60 and 70). In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level

of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

5. Claims 60-62, 68, 70-72, 76 and 78-86 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson/
Primary Examiner, Art Unit 1652